NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL COMPANY LIMITED et al., Plaintiffs, v. NORWICH PHARMACEUTICALS, INC. et al., Defendant.	:	**Civil Action No. 20-8966 (SRC)** **OPINION & ORDER**

CHESLER, District Judge

This matter comes before the Court on the application for claim construction by Plaintiffs Takeda Pharmaceutical Company Limited and Takeda Pharmaceuticals U.S.A. Inc. (collectively, "Takeda") and Defendant Norwich Pharmaceuticals, Inc. ("Norwich.") In this Court's Opinion and Order, dated March 3, 2022 ("the March 3 Opinion"), the Court Ordered supplemental briefing on the construction of two disputed terms:

> A second phase of claim construction will be needed to complete the construction of two disputed terms. The parties must further brief the question of the ordinary meaning of Term 4, "limited." . . . Also, Defendant shall submit a supplementary brief which proposes a particular construction of the ordinary meaning of "C_{max} which results in euphoria." This Court will complete the claim construction of those two terms after supplementary briefing has been completed.

(Opinion and Order of March 3, 2022 at 25.) The Court now considers the supplemental briefing on these two terms.

I. **"Limited bioavailability"**

Term 4 appears in claims 1 and 18 of the '735 patent:

1. A pharmaceutical composition comprising an unprotected prodrug and one or more pharmaceutically acceptable additives;

   wherein said prodrug consists of L-lysine-d-amphetamine or a pharmaceutically acceptable salt thereof;

   wherein said composition is in a form suitable for oral administration;

   wherein said composition provides release of amphetamine as an active from said prodrug following oral administration;

   and wherein said prodrug has **limited bioavailability of amphetamine when administered through alternative routes of administration**.

18. An oral pharmaceutical dosage form for the administration of amphetamine comprising an unprotected prodrug and one or more pharmaceutically acceptable additives;

   wherein said prodrug consists of L-lysine-d-amphetamine or a pharmaceutically acceptable salt thereof;

   wherein said composition provides **limited** release of amphetamine as an active from said prodrug following oral administration;

   and wherein said prodrug has **limited bioavailability of amphetamine when administered through alternative routes of administration**.

Defendant had contended that this phrase has its ordinary meaning, but offered no interpretation of what that ordinary meaning is. Plaintiffs proposed this construction: "lower extent of absorption of the amphetamine released following administration of L-lysine-d-amphetamine or a salt thereof through parenteral routes of administration often employed in illicit use compared to the extent of absorption of d-amphetamine following administration of a comparable molar dose of d-amphetamine or a salt thereof through parenteral routes of administration often employed in illicit use." In short, this Court rejected Plaintiffs' proposed construction and

accepted Defendant's view that the phrase has its ordinary meaning, and the Court Ordered supplemental briefing to determine the ordinary meaning of the key term, "limited."

Furthermore, in the March 3 Opinion, this Court expressed skepticism about, in particular, Plaintiffs' arguments that "limited" meant "lower" in the context of a comparison with the effects of administration of d-amphetamine by alternative routes. The supplemental briefing, however, has persuaded the Court to reconsider, since Defendant has proposed a construction that cannot be correct. Its defects help Plaintiffs make their case.

In the supplemental briefs, the parties begin with two important points of agreement. First, they agree that the ordinary meaning of "limited" is "restricted in extent." Second, they agree that this construction, alone, is not enough; something more is needed by the skilled artisan to understand the nature of the limit, and both parties look to the specification to understand it more fully.[1] It is at this point that their paths diverge. While Plaintiffs use different language than presented in their original claim construction brief, the ideas remain the same: "limited" further requires that the bioavailability of amphetamine be lower than that produced by alternative administration of d-amphetamine. Defendant proposes that "limited" further requires that the bioavailability of amphetamine be a small number.

The problem for Defendant is: what is a small number? Defendant has nothing more to say about what a small number is, nor about how the skilled artisan would know what is a small number and what is not. Defendant's construction, from the outset, appears ambiguous and

[1] "[T]he person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." Phillips v. AWH Corp., 415 F.3d 1303, 1313 (Fed. Cir. 2005).

incomplete.

Defendant contends that a key point of disagreement between the parties is the question of magnitude, and that Plaintiffs' construction is "silent on magnitude," whereas Defendant proposes that "limited" means both "restricted in extent" and that the magnitude of the extent is "small." Plaintiffs argue that "'limited' requires a comparison to establish the boundaries within which a given parameter is 'limited.'" (Pls.' Supp. Br. 3.) Defendant thus is incorrect in asserting that Plaintiffs are silent on magnitude. Plaintiffs address the issue of magnitude in a different way from Defendant and with more persuasive results. In short, Plaintiffs contend that the magnitude is limited to values lower than those produced by a comparator, d-amphetamine.

In the March 3 Opinion, this Court noted that, while the '735 patent has much to say on the subject of the functionality of the invention related to limited bioavailability, it might be useful to examine the double use of the word "limited" in claim 18. Claim 18 is particularly interesting because the word "limited" appears in two different phrases, "limited release of amphetamine" and "limited bioavailability of amphetamine." "Because claim terms are normally used consistently throughout the patent, the usage of a term in one claim can often illuminate the meaning of the same term in other claims." Phillips, 415 F.3d at 1314.

In short, Takeda argues persuasively that the construction of "limited," as it appears in the claim 18 phrase, "limited release of amphetamine as an active from said prodrug following oral administration," can inform our understanding of "limited bioavailability." Plaintiffs argue:

> In the context of "limited release," it is not that the "release" is reduced to a "very low amount of d-amphetamine released into circulation." (ECF No. 173 at 13). This would be contrary to the teachings of the specification to release a therapeutically effective amount of d-amphetamine from LDX. (See, e.g., Ex. 2, '735 patent at 10:59-61, 12:17-22). Rather, "limited release" refers to a rate of release that is restricted compared to d-amphetamine alone. Thus, "limited" is

> used in a consistent manner in the context of both "limited release" and "limited bioavailability."

(Pls.' Supp Br. 1-2.)

The specification puts the meaning of "limited," as used in both "limited bioavailability" and "limited release," into context. After an initial statement incorporating by reference other patent documents, the "Detailed Description of the Invention" subsection begins as follows:

> The invention utilizes covalent modification of amphetamine to decrease its potential for causing overdose or abuse. The amphetamine is covalently modified in a manner that decreases its pharmacological activity, as compared to the unmodified amphetamine, at doses above those considered therapeutic. When given at lower doses, such as those intended for therapy, the covalently modified amphetamine retains pharmacological activity similar to that of the unmodified amphetamine.

'735 patent, col.8 ll.59-67. Here, the specification expressly compares the pharmacological activity of the inventive composition, covalently modified amphetamine, to that of unmodified amphetamine. The specification explains that, at therapeutic doses, the pharmacological activity of the administered prodrug is "similar" to that of the unmodified amphetamine, whereas, at doses higher than therapeutic doses, the pharmacological activity "decreases," relative to that of unmodified amphetamine. While the word "limited" does not appear in the quote, the specification here defines the invention as using covalent modification to reduce the pharmacological activity of amphetamine, compared to unmodified amphetamine, when administered at higher-than-therapeutic doses. This definition of the invention is consistent with Plaintiffs' understanding of "limited" in claims 1 and 18, and provides the context for the express disclosure of limiting release that directly follows.

In the next paragraph, the specification states: "[O]verdose protection results from a natural gating mechanism at the site of hydrolysis that **limits the release** of the active

amphetamine from the prodrug at greater than therapeutically prescribed amounts." '735 patent, col.9 ll.8-11 (emphasis added.) The specification thus uses the phrase, "limits the release," in proposing a theory about the decreased pharmacological activity of the inventive composition, relative to that of unmodified amphetamine at doses higher than therapeutic doses. Note that, contrary to Defendant's construction of the meaning of "limited," the specification does not characterize this limited release as "small" in magnitude. Instead, the magnitude of the limited release is given meaning by comparison to the unlimited release of unmodified amphetamine. The specification teaches that the limit operates so as to decrease the release from the prodrug when administered at doses higher than therapeutic doses, but not to affect the release from the prodrug when administered at therapeutic doses. "Restricted in extent to a small amount" does not capture the complexity of what the patentees had to say about "limited release" in the specification. Rather, Plaintiffs are correct that the specification teaches that "'limited release' refers to a rate of release that is restricted compared to d-amphetamine alone." (Pls.' Supp. Br. 2.)

As this discussion shows, construing "limited release" in claim 18 as "restricted to a small magnitude" fails to express what the specification teaches about limiting the release of amphetamine in the inventive composition. As already stated, Defendant's contention that the restricted extent is small is ambiguous and uninformative. "Small" is meaningful as a relative term; a point of comparison or context is needed to make it meaningful. Unwittingly, Defendant has proposed a construction with a defect that suggests that Plaintiffs were right all along about the need for a comparator.

Second, the discussion of the meaning of "limited release" in the context of the

specification shows that the restriction in extent of "limited" implies a comparison to the absence of limitation associated with the effects of unmodified amphetamine. Because the specification makes the comparison explicit, the Court agrees with Plaintiffs that "limited release" in claim 18 implies a comparator. The specification expressly compares the limited release of amphetamine from the prodrug to the unlimited release of unmodified amphetamine, and the skilled artisan would understand this in reading claim 18 in the context of the specification.

Next, the Court considers the construction of "limited" in claims 1 and 18, in regard to its use in the phrase, "limited bioavailability of amphetamine when administered through alternative routes of administration." As to alternative routes of administration,[2] the Abstract states: "Further, compounds and compositions of the invention decrease the bioavailability of amphetamine by parenteral routes, such as intravenous or intranasal administration, further limiting their abuse liability." This statement in the Abstract applies to the entire invention, in all embodiments, and it supports Plaintiffs' understanding of "limited bioavailability:" it requires only that bioavailability of amphetamine, administered through parenteral routes, be decreased.[3] The use of the word "decreased" raises the question: decreased from what?

Plaintiffs contend that the decrease that is characteristic of the limited bioavailability found with parenteral administration of the inventive composition should be understood in reference to the unlimited bioavailability that would be found with parenteral administration of

[2] The parties agreed that "alternative routes of administration" means "parenteral routes of administration often employed in illicit use."

[3] Similarly, the "Summary of the Invention" states: "Covalent attachment of a chemical moiety to amphetamine can decrease its pharmacological activity when administered through injection or intranasally." '735 patent, col.4 ll.6-8. Again, this statement about the invention is not limited to a particular embodiment and describes only decreased pharmacological activity when the inventive composition is administered by two alternative routes.

unbound amphetamine. There is much intrinsic evidence that supports this. Defendant, in fact, while arguing against Plaintiffs' use of d-amphetamine as an implied comparator, relies on Examples 11 and 12 in the specification – both of which expressly use d-amphetamine as the comparator. Examples 11 and 12 refer to the data in Figures 11 and 12, and those figures expressly compare concentration of d-amphetamine to LDX.

In fact, the patent uses unmodified amphetamine as a comparator to the inventive composition in many places. The patent expressly compares the effects of the inventive composition to those of "unbound amphetamine" in claims 2, 11, 13, and 17; claim 10 compares such effects to those of "amphetamine alone." Claim 11 refers to the bioavailability of the inventive composition in the context of a comparison to unbound amphetamine:

> 11. The pharmaceutical composition of claim 1, wherein said L-lysine-d-amphetamine or pharmaceutically acceptable salt thereof is in an amount sufficient to maintain a steady-state serum release curve of amphetamine which provides a therapeutically effective bioavailability of amphetamine but prevents spiking or increased blood serum concentrations compared to unbound amphetamine.

The parties have agreed that, in the context of claims 1 and 18, "bioavailability" means "extent of absorption." Claim 13 expressly compares the rate of absorption of the inventive composition to that of unbound amphetamine:

> 13. The pharmaceutical composition of claim 1, wherein said L-lysine-d-amphetamine or pharmaceutically acceptable salt thereof is in an amount sufficient to provide a therapeutically effective amount of amphetamine, but at a reduced rate of absorption of the amphetamine as compared to unbound amphetamine.

The intrinsic evidence thus supports construing "limited bioavailability," similarly to "limited release," as implying a comparison to the effects of unbound amphetamine.

Having found that the patent frequently compares the effects of the inventive composition

to the effects of unmodified amphetamine, both expressly and implicitly, the Court returns to the relevant description of the invention in the Abstract: "Further, compounds and compositions of the invention decrease the bioavailability of amphetamine by parenteral routes, such as intravenous or intranasal administration, further limiting their abuse liability." As discussed, the Detailed Description of the Invention in the specification further explains that the covalent modification of amphetamine "decreases its pharmacological activity, as compared to the unmodified amphetamine, at doses above those considered therapeutic." '735 patent, col.8 ll.61-64. These statements about the invention as a whole thus define the invention as providing decreased bioavailability of amphetamine, compared to unmodified amphetamine, when administered by parenteral routes.

The specification does not say anything different about the invention as a whole. Rather, the specification describes particular embodiments which decrease the bioavailability of amphetamine from parenteral administration to a greater degree, as in Examples 11 and 12, which state that bioavailability was "substantially decreased." Nonetheless, the Federal Circuit has cautioned courts about importing claim limitations from specific embodiments: "although the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments." Phillips, 415 F.3d at 1323. Careful examination of the specification shows no statements which manifestly restrict the invention, as a whole, to embodiments in which the bioavailability of amphetamine from parenteral administration is substantially decreased. Nor does Norwich argue that the substantial decrease of bioavailability which appears in Examples 11 and 12, and at other places in the specification, manifestly restricts the invention and should be imported as a claim

limitation. See Liebel-Flarsheim Co. v. Medrad, Inc., 358 F.3d 898, 906 (Fed. Cir. 2004) ("Even when the specification describes only a single embodiment, the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction.")

Instead, the specification makes clear that such a substantial limitation in bioavailability after parenteral administration may be a characteristic of a particular embodiment, rather than the invention as a whole. For example, the specification states:

> Another embodiment of the invention is a composition for preventing a C_{max} spike for amphetamine when taken by means other than orally while still providing a therapeutically effective bioavailability curve if taken orally comprising an amphetamine which has been covalently bound to a chemical moiety.

'753 patent, col.12 ll.46-51. In the "Summary of the Invention," the specification states:

> Covalent attachment of a chemical moiety to amphetamine can decrease its pharmacological activity when administered through injection or intranasally. . . . In one embodiment, the composition provides oral bioavailability which resembles the pharmacokinetics observed for extended release formulations. In another embodiment, release of amphetamine is diminished or eliminated when delivered by parenteral routes.

'753 patent, col.4 ll.6-19. Note that the first sentence in this paragraph, which could be read as a statement of general application, refers only to decreasing pharmacological activity when administered through alternative routes. The last sentence, which describes an embodiment, describes the release of amphetamine as "diminished or eliminated." This makes clear that the specification does not restrict the invention as a whole beyond the requirement that pharmacological activity of amphetamine, when administered by a parenteral route, be "decreased," although a particular embodiment may eliminate amphetamine release entirely.

Norwich, in its supplementary opposition, argues that Takeda's use of a comparator "is

an improper attempt to read preferred embodiments from the specification into the claims." (Def.'s Resp. Supp. Br. 4.) This is incorrect. As shown in the analysis just offered, there is abundant intrinsic evidence that the inventors defined the invention by comparing the effects of their covalently modified amphetamine to those of unmodified amphetamine; this is not a characteristic of only some embodiments. The patent repeatedly makes the comparison expressly and broadly. In the context of "limited bioavailability" in claims 1 and 18, the need for a comparator arises from the need to make "limited" meaningful to the skilled artisan in the context of both the claim language and the specification, both to understand the claim term, "limited bioavailability," as well as "limited release" in claim 18. To the contrary, it is Norwich that proposes a construction that attempts to read the substantial decrease characteristic of various embodiments in the specification into the claims.

The Court concludes that it must reconsider the statements made in the March 3 Opinion which criticized Plaintiffs' use of "lower" in their proposed construction of "limited." Plaintiffs were correct in arguing that the claim term "limited bioavailability" in claims 1 and 18 requires only lower bioavailability. The specification describes a variety of embodiments, some of which manifest a substantial decrease in bioavailability, and some of which manifest merely a decrease. No statement manifestly restricts the entire invention to compositions which produce a substantial decrease in bioavailability. Furthermore, having concluded that "limited bioavailability" means "lower bioavailability," as Plaintiffs contended, this raises the question: lower than what? For all the reasons explained, the Court concludes that "limited bioavailability," in claims 1 and 18, implies a comparison to the unlimited bioavailability that occurs in the context of parenteral administration of unmodified amphetamine; "lower

bioavailability" means lower than the bioavailability of unmodified amphetamine found with parenteral administration.

Thus, this Court concludes that it erred in rejecting Plaintiffs' proposed construction of "limited bioavailability," and that Plaintiffs' original proposed construction is the correct one. In claims 1 and 18, "limited bioavailability" is construed to mean: "lower extent of absorption of the amphetamine released following administration of L-lysine-d-amphetamine or a salt thereof through parenteral routes of administration often employed in illicit use compared to the extent of absorption of d-amphetamine following administration of a comparable molar dose of d-amphetamine or a salt thereof through parenteral routes of administration often employed in illicit use."

II. **"C_{max} which results in euphoria"**

Term 6, "C_{max} which results in euphoria," appears in claim 11 of the '486 patent and claim 10 of the '735 patent. Although the parties had agreed that the term had its ordinary meaning, Defendant had not proposed a particular construction, and the Court Ordered that Norwich do so. Norwich submitted a supplementary brief, and Takeda submitted a response to it.

The parties dispute only the ordinary meaning of "euphoria." Defendant contends that "euphoria" is "an extreme state of perceived well-being," while Plaintiffs contend that it is "a feeling of well-being." Thus, the parties dispute whether "euphoria" refers to a state of well-being, or an extreme state of well-being. In support of their proposed constructions, both parties start with dictionary definitions, and then move to intrinsic evidence. Such approaches are inconsistent with Federal Circuit law. As the Federal Circuit recently stated: "When the

meaning or scope of a patent claim is disputed by litigants . . . the court looks first to the intrinsic record of the patent document." Nature Simulation Sys. Inc. v. Autodesk, Inc., 23 F.4th 1334, 1339 (Fed. Cir. 2022). This Court begins with the intrinsic record, not the dictionaries.

The claims at issue state:

> 11. The method of claim 6, wherein the L-lysine-d-amphetamine or salt thereof is in an amount sufficient to provide a therapeutically bioequivalent AUC when compared to amphetamine alone, but does not provide a C_{max} which results in euphoria. ('486 patent.)
>
> 10. The composition of claim 9, wherein said L-lysine-d-amphetamine or pharmaceutically acceptable salt thereof is in an amount sufficient to provide a therapeutically bioequivalent area under the curve (AUC) of amphetamine when compared to amphetamine alone, but in an amount insufficient to provide a C_{max} which results in euphoria. ('735 patent.)

Both claims contrast an AUC for amphetamine that provides a therapeutic effect, with a C_{max} that results in euphoria.

The parties agree on one important point: any euphoric effect of the drug is undesirable. Defendant contends that the intrinsic evidence describes "euphoria as an undesired effect." (Def.'s Supp. Br. 2.) Takeda contends that "*any* euphoria caused by the drug . . . is undesirable." (Pls.' Supp. Resp. Br. 3.)

This Court finds that both parties' proposed constructions are problematic. Consider the disclosure in the specification of an embodiment that *prevents* euphoria:

> Another embodiment of the invention provides a method for delivering amphetamine dosage which prevents euphoria, comprising administering to a patient in need a composition formulated for oral dosage comprising amphetamine covalently attached to a chemical moiety wherein said blood levels of amphetamine maintain a therapeutically effect level but do not result in a euphoric effect.

'735 patent, col.4 ll.57-63. If Plaintiffs' proposed construction is correct, then there is at least

one embodiment which is a method for delivering amphetamines which *prevents* a feeling of well-being. It seems unlikely that the inventors actually invented a method of delivering amphetamine which prevents a state of well-being.[4] This weighs against adopting Plaintiffs' proposed construction.

Defendant proposes that euphoria is an extreme state. Takeda, however, points out that the intrinsic evidence supports the idea that there are degrees of euphoria. The specification states: "For each of the recited methods, the composition may yield a therapeutic effect without substantial euphoria." '735 patent, col.19 ll.32-33. Similarly, euphoric effect can be "reduced." '735 patent, col.14 ll.38-39. These support Takeda's contention that there are degrees of euphoria; it is not a single, extreme point on the continuum of feelings of well-being.

On this record, this Court finds that both proposed constructions are problematic, and that the meaning of "euphoria" should be in the middle of the two proposed constructions. Because the patent recognizes degrees of euphoria, it cannot be the extreme of the state of well-being, as Defendant proposes. Because the parties agree that *any* euphoric effect is undesirable, it cannot be an ordinary feeling of well-being. The construction of "euphoria" that best fits the intrinsic

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[4] The Federal Circuit has held:

> Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim. The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction. A claim construction is persuasive, not because it follows a certain rule, but because it defines terms in the context of the whole patent.

Renishaw PLC v. Marposs Societa' Per Azioni, 158 F.3d 1243, 1250 (Fed. Cir. 1998) (citations omitted).

evidence is "an exaggerated feeling of well-being."[5] Such a feeling can exist in degrees, is undesirable as an effect of a pharmaceutical, and is consistent with the specification's description of an embodiment that prevents euphoria.

In conclusion, the Court construes "limited bioavailability" to mean: "lower extent of absorption of the amphetamine released following administration of L-lysine-d-amphetamine or a salt thereof through parenteral routes of administration often employed in illicit use compared to the extent of absorption of d-amphetamine following administration of a comparable molar dose of d-amphetamine or a salt thereof through parenteral routes of administration often employed in illicit use." The meaning of "euphoria" is "an exaggerated feeling of well-being."

SO ORDERED.

s/ Stanley R. Chesler
STANLEY R. CHESLER, U.S.D.J.

Dated: April 21, 2022

[5] This construction is similar to the definition of euphoria in the Merriam-Webster Medical Dictionary, cited by both parties: "a feeling of well-being or elation, *especially*: one that is groundless, disproportionate to its cause, or inappropriate to one's life situation."